Risk Factors of Delayed Methotrexate Elimination after Receiving High-dose Methotrexate Therapy

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Background & Aims

- High-dose methotrexate (HDMTX) (doses≥ 1g/m^2) is pivotal chemotherapy in the treatment of patients with various cancers such as Burkitt's lymphoma.
- Even when guideline strictly followed and maintaining adequate urine alkylation and hydration, high proportion of patients suffering from delayed MTX elimination that attributed to systemic toxicities such as nephrotoxicity, hemotoxicity, and hepatotoxicity.
- This single-center study aimed to explore predictors of delayed MTX elimination.

Methods

- **Study design and settings:** Retrospective study conducted in one medical center in Southern Taiwan July 2014 to August 2019.
- **Patient population:** Patients received HDMTX intravenously were included without age restriction. Patients without testing serum MTX level, with insufficient data of MTX regimen, or unable to access delay or not were excluded.
- **Equipment:** Serum MTX concentrations were tested using the Abbott ARCHITECT i2000SR chemiluminescence enzyme immunoassay (Abbott Diagnostics, Abbott Park, IL, USA)
- **Definition:** Plasma MTX concentrations 24h (T24), 48h (T48), 72h (T72), and 96h (T96) after administration were used as indices of MTX elimination. Delayed MTX clearance was defined as a serum MTX concentration ≥ 10 μmol/L at 24 h, 1 μmol/L at 48 h, 0.1 μmol/L at 72 h, and/or 0.05 μmol/L at 96 h after starting administration.
- **Outcomes:** Primary outcome was to find independent factors related to delayed MTX elimination. Clinical characteristics, disease type, and recue therapy used in patients with or without delayed MTX elimination were presented and compared with chi-square test, Fisher's exact test, or Mann-whitney u test as appropriate.
- **Statistical analysis:** To test the independence of the risk factors related to delayed MTX elimination, the significant variables (*P* <.05) in the univariate analyses were entered into a multivariate logistic regression model with stepwise selection of independent variables. All statistical analyses were conducted by SAS 9.4.

Results

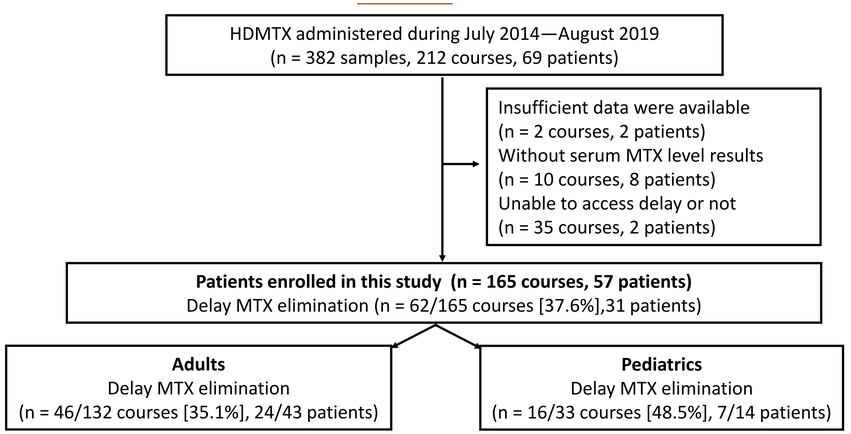

Figure 1. Enrollment of study patients

Results

Table 1. Baseline characteristics between patients with or without delay MTX elimination.

Variables	All courses (N = 165)	Delay (N = 62)	Non-delay (N = 103)	*P*-value
Age (years)	44.6 ± 22.9	45.9 ± 22.4	43.8 ± 23.2	0.569
Male	100 (60.6)	47 (75.8)	53 (51.5)	**0.003**
BMI	23.2 ± 5.1	24.1 ± 4.9	22.6 ± 5.1	0.059
BSA	1.6 ± 0.4	1.7 ± 0.3	1.5 ± 0.4	**0.006**
Diabetes mellitus	36 (21.8)	9 (14.5)	27 (26.2)	0.084
Cancer				
B cell lymphoma	115 (69.7)	37 (59.7)	78 (75.7)	0.091
T cell lymphoma	31 (18.8)	17 (27.4)	14 (13.6)	
Osteosarcoma	14 (8.5)	5 (8.1)	9 (8.7)	
Others	5 (3.0)	3 (4.8)	2 (1.9)	
Baseline condition				
Albumin (g/dL) (N = 68)	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	0.663
GOT (U/L) (N = 158)	28.2 ± 16.9	27.7 ± 10.9	28.5 ± 19.8	0.742
GPT (U/L) (N = 163)	41.3 ± 35.9	47.6 ± 35.3	37.5 ± 35.8	0.082
Total bilirubin (mg/dL) (N = 130)	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.623
White blood cell (K/μL) (N = 165)	7.0 ± 5.1	8.0 ± 4.4	6.4 ± 5.3	0.051
Red blood cell (M/μL)	3.7 ± 0.7	3.7 ± 0.8	3.7 ± 0.6	0.772
Platelet (K/μL) (N = 164)	261.6 ± 131.9	269.2 ± 117.2	257.1 ± 140.3	0.571
Hemoglobin (g/dL)	10.9 ± 2.0	11.0 ± 2.3	10.8 ± 1.8	0.701
eGFR (mL/min 1.73 m^2)	99.6 ± 31.0	90.7 ± 32.1	104.9 ± 29.1	**0.004**
Third space fluid	15 (9.1)	11 (17.7)	4 (3.9)	**0.004**
Diarrhea	15 (9.1)	12 (19.4)	3 (2.9)	**0.001**
AKI or delay elimination after prior cycle	55 (33.3)	31 (50.0)	24 (23.3)	**0.001**
MTX regimen				
Cycle (N = 199)	2.7 ± 1.9	2.8 ± 1.9	2.7 ± 1.9	0.621
MTX infusion time (h)	9.9 ± 9.1	9.8 ± 9.1	9.9 ± 9.2	0.987
Receive MTX IT	44 (26.7)	18 (29.0)	26 (25.2)	0.592
Dose of MTX IT (mg)	4.4 ± 7.6	4.6 ± 8.2	4.3 ± 7.3	0.774
BSI based MTX dosing (g/m^2)	4.4 ± 2.5	4.4 ± 2.1	4.4 ± 2.8	0.973
Cumulative MTX dose (g) (N = 164)	14.7 ± 20.0	15.7 ± 18.6	14.0 ± 20.9	0.600
Recue regimen				
First MTX TDM >72 h	40 (24.2)	16 (25.8)	24 (23.3)	0.712
BSI based leucovorin dosing (mg/m^2/day)	90.9 ± 64.3	96.8 ± 66.7	87.3 ± 63.0	0.362
Leucovorin frequency (times/day)	5.1 ± 1.8	5.4 ± 1.9	4.9 ± 1.6	**0.047**
Insufficient leucovorin dose	27 (16.4)	17 (27.4)	10 (9.7)	**0.004**
Complete urine alkalinization	61 (37.0)	20 (32.3)	41 (39.8)	0.406
Bicarbonate dose (mg/day)	98.2 ± 39.9	97.4 ± 44.4	98.7 ± 37.1	0.843
Hydration amount (L/m^2/day)	1.6 ± 0.7	1.5 ± 0.5	1.7 ± 0.8	0.099
Urine pH level (N = 74)	7.0 ± 1.1	7.0 ± 1.6	6.9 ± 0.5	0.706
Concomitant medications				
Total drug interaction number	1.2 ± 1.0	1.5 ± 1.1	1.1 ± 0.9	**0.021**
Drug increase MTX level	71 (43.0)	35 (56.5)	36 (35.0)	**0.009**
Nephrotoxic drugs	108 (65.5)	43 (69.4)	65 (63.1)	0.500
NSAID	10 (6.1)	4 (6.5)	6 (5.8)	1.000
Penicillin	16 (9.7)	10 (16.1)	6 (5.8)	0.054
Proton pump inhibitor	48 (29.1)	22 (35.5)	26 (25.2)	0.215
Hydrochlorothiazide	8 (4.8)	6 (9.7)	2 (1.9)	0.054
Sulfa drug	47 (28.5)	21 (33.9)	26 (25.2)	0.286
Aminoglycoside	8 (4.8)	5 (8.1)	3 (2.9)	0.153
Ciprofloxacin	4 (2.4)	0 (0.0)	4 (3.9)	0.298
Vancomycin	6 (3.6)	2 (3.2)	4 (3.9)	1.000
ACEI or ARB	16 (9.7)	7 (11.3)	9 (8.7)	0.597
Diuretic with urinary acidification	14 (8.5)	10 (16.1)	4 (3.9)	**0.009**
Allopurinol	26 (15.8)	8 (12.9)	18 (17.5)	0.512
Acyclovir	3 (1.8)	1 (1.6)	2 (1.9)	1.000

Data are presented as median (interquartile range) or N (%).
ACE I, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; IT, intrathecal; IV, intravenous; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; TDM, therapeutic drug monitoring.

Table 2. Key factors related to delayed MTX elimination

Variables	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*P*-value	aOR (95% CI)[1]	*P*-value
Male	2.96 (1.47–5.94)	**0.002**	3.92 (1.70–9.04)	**0.001**
Body surface area	3.52 (1.27–9.75)	**0.015**		
Creatinine clearance	0.98 (0.97–1.00)	**0.005**	0.98 (0.97–1.00)	**0.010**
Third space fluid	5.34 (1.62–17.60)	**0.006**		
Diarrhea	8.00 (2.16–29.65)	**0.002**	14.27 (3.42–59.60)	**<.001**
AKI or delay elimination after prior cycle	3.29 (1.67–6.47)	**0.001**	3.06 (1.38–6.80)	**0.006**
Total drug interaction number	1.47 (1.07–2.03)	**0.017**		
Penicillin	3.11 (1.07–9.03)	**0.037**	4.64 (1.28–16.87)	**0.020**
Diuretic with urinary acidification	4.76 (1.42–15.91)	**0.011**		

Odds ratio are calculated by logistic regression. [1] aOR: djusted odds ratios are calculated by multivariate logistic regression and adjusted for factors with a *P*-value <0.05 in the univariate analysis.

Conclusions

- More than 35% of patients suffer from delayed MTX elimination after receiving HDMTX ether in adults or pediatrics. Male gender, lower baseline creatinine clearance, diarrhea, acute kidney injury or delay elimination at prior cycle, and concurrent use of penicillin may increase risk of delayed MTX elimination. Knowing these factors make patients safer to receive HTMTX to prevent systematic toxicity.